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10/757,708	01/14/2004	Derek O' Hagan	PP-19768.002	3852

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 05/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,708	O' HAGAN ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48,50,52-64,69 and 72-89* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,8-10,12,13,15-18,23,26-31,34-42,44-48,50,52-55,61,69,76-79 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 4,7,11,14,19-22,24,25,32,33,43,56-60,62-64,72-75,80-85 and 87-89.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of the invention of Group II, drawn to microparticles comprising a biodegradable polymer, a surfactant, a first polynucleotide-containing species and a second species adsorbed to the microparticles,and of the species of PLGA, pCMV, 10-20%, 0.5-2 wt% cationic surfactant, CpG, CTLK immune response, and adsorbed immunological adjuvant, in the reply filed on 05/10/2006 is acknowledged. The traversal is on the ground(s) that Groups I-V are classified in the same class and subclass and therefore searches for the different groups are co-extensive and a search and examination of the entire application can be made without a serious burden. Accordingly, Applicants request withdrawal of the restriction requirement. This is not found persuasive for the reasons of record in the restriction requirement of 03/10/2006. To wit, in addition to meeting the requirements of restriction under 35 U.S.C. 121, each Group has different compositions with different structural considerations which are non-coextensive, and lead to a serious burden to the Examiner to search and examine these groups together. Applicants arguments that the examiner must show burden of searching by separate classification and separate status in the art are not persuasive because classification is a very broad grouping of inventions and distinct and different inventions are present in a particular class/subclass. Additionally, the different inventions have a different status in the art because they are drawn to compositions that are structurally different. For example, the

invention of Group I is drawn to a composition comprising a species entrapped within the microparticles, the invention of Group II is drawn to a species adsorbed to microparticles, the invention of Group III is drawn to microparticles in which the first protion of the cationic surfactant is bound to the biodegradable polymer, and the second portion forms a comples with the first polynucleotide-containing species, the invention of Group IV is drawn to a composition comprising the microparticles comprising a biodegradable polymer, a surfactant, a first polynucleotide-containing species and additional microparticles with an immunological adjuvant adsorbed onto their surface, and the invention of Group V is drawn to a composition comprising two different microparticles comprising a biodegradable polymer, a surfactant, a first polynucleotide-containing species and additional microparticles with an immunological adjuvant entrapped within. Applicants argue that search for one group would necessarily identify art for the other groups. This is not found persuasive because these different structures require distinct searches in the art. Therefore these distinct groups and species require separate and non-coextensive searches in the patent and non-patent literature and both search and examination of all the inventions and species will be a burden. Hence, restriction is proper. The requirement is still deemed proper and is therefore made FINAL. However, upon further consideration, the election between the species recited in claims 27-30 is withdrawn.

Claims 49, 51, 65-68, 70, and 71 have been cancelled. New claims 72-89 were added. No new matter was introduced by the new claims.

Claims 4, 7, 11, 14, 19-22, 24, 25, 32, 33, 43, 56-60, 62-64, 72-75, 80-85, and 87-89 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions or species, there being no allowable generic or linking claim.

Claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 23, 26, 27-31, 34-42, 44-48, 50, 52-55, 61, 69, 76-79, and 86 are pending.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-3, 5, 6, 9, 10, 12, 13, 15-18, 23, 26, 28-31, 34-42, 44-48, 50, 52-55, 61, 69, 76-79, and 86 are rejected on the ground of nonstatutory obviousness-type double

patenting as being unpatentable over claims 1, 5-19, 24-26, and 35-40 of U.S. Patent No. 6,884,435. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to (i) microparticles comprising a biodegradable polymer, a cationic lipid, and a first polynucleotide-containing species adsorbed on the surface of the microparticles, wherein the first polynucleotide species constitute at least 5% of the total weight of the microparticles, the cationic surfactant is cetyltrimethylammonium bromide (CTAB), the biodegradable polymer is poly(lactide-co-glycolide) (PLG), the first polynucleotide-containing species encodes for an antigen derived from a pathogenic organism such as HIV, the microparticles further comprise an adsorbed immunological adjuvant such as CpG (claims 1-3, 5, 6, 9, 10, 12, 13, 15-18, 23, 26, 29, 30, 34-37, 69, 76-79, and 86), (ii) a method of producing the microparticles by obtaining a w/o/w emulsion comprising the polymer and the surfactant, removing the organic solvent from the solution and adsorbing the first polynucleotide-containing species to the microparticles (claims 31 and 52-55), (iii) a method of delivering a therapeutic amount of polynucleotide to a host animal (claim 38), (iv) a method of treating a pathogenic infection (claim 40), and (iv) a method of stimulating an immune response, wherein the immune response comprises a CTL immune response (claims 39, 41, 42-48, and 50).

The patent claims recite (i) a microparticle comprising a polymer such as PLG, a cationic detergent such as CTAB, and an antigen comprising a polynucleotide such as plasmid (example 7 discloses that the plasmid is pCMV) adsorbed on the

surface of the microparticle, wherein the polynucleotide encodes for an antigen derived from a pathogenic organism such as HIV and wherein the microparticle is formed in the presence of the detergent and then exposed to the polynucleotide (the specification defines that a w/o/w solvent evaporation system can be used to form the microparticles, see column 13, lines 10-39); the microparticles further comprise CpG as an immunological adjuvant (claims 1, 5-13, 16, 17, 19, 20, 24-26, 35-37) and (ii) a method for raising an immune response by administering the microparticles to a vertebrate animal (the specification discloses that the intent of delivery is to use the particle as a vaccine to elicit an immune response in a vertebrate and to treat a disease, see column 4, lines 3-30; additionally the specification defines that a vertebrate can be a human, column 8, lines 45-52) (claims 38-40). The specification discloses that the polynucleotide can constitute 5% or 0.1 to 10% of the total weight of the microparticle (column 14, lines 6-10) and that the microparticles comprise 0.1 to 10% or 0.5 to 2 % cationic surfactant (column 13, lines 30-37). With respect to the limitation of the adjuvant being adsorbed on the surface of the microparticle, the specification discloses that adjuvants can be used to enhance the immunogenicity of the microparticles and that the adjuvants can be adsorbed on the microparticles (column 14, lines 36-51). With respect to the limitation recited in claim 3, the specification discloses that the microparticles have a diameter of about 200 nm to about 30 μm that includes the range recited by claim 3 (column 5, lines 1-10). Thus, the patent claims 1, 5-19, 24-26, and 35-40 anticipate claims 1-3, 5, 6, 9, 10, 12, 13, 15-18, 23, 26, 28-31, 34-42, 44-48, 50, 52-55, 61, 69, 76-79, and 86 of the instant application. Since the US Patent No.

6,884,435 claims 1, 5-19, 24-26, and 35-40 embrace all limitation of the instant claims, the patent claims and the instant claim are obvious variants of one another.

Claims 1-3, 5, 6, 9, 10, 12, 13, 15-18, 23, 26, 28-31, 34-37, 52-55, 61, 69, 76-79, and 86 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 8, 10, 11, 13, 15-21, 24-27, 30, and 31 of U.S. Application No. 11/113,861. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to (i) microparticles comprising a biodegradable polymer, a cationic lipid, and a first polynucleotide-containing species adsorbed on the surface of the microparticles, wherein the first polynucleotide species constitute at least 5% of the total weight of the microparticles, the cationic surfactant is CTAB, the biodegradable polymer is PLG, the first polynucleotide-containing species encodes for an antigen derived from a pathogenic organism such as HIV, the microparticles further comprise an adsorbed immunological adjuvant such as CpG (claims 1-3, 5, 6, 9, 10, 12, 13, 15-18, 23, 26, 29, 30, 34-37, 69, 76-79, and 86), (ii) a method of producing the microparticles by obtaining a w/o/w emulsion comprising the polymer and the surfactant, removing the organic solvent from the solution and adsorbing the first polynucleotide-containing species to the microparticles (claims 31 and 52-55).

The application claims recite (i) a microparticle comprising a biodegradable polymer such as PLG, a cationic detergent, an immunological adjuvant and a polynucleotide, wherein both the immunological adjuvant and the polynucleotide

are adsorbed on the surface of the microparticle and wherein the polynucleotide encodes for an antigen derived from a pathogenic organism or tumor (claims 1-5, 8, 10, 11, 36-38, 40-42, 45, and 46) and (ii) a method of producing a microparticle by providing an emulsion comprising an organic solvent, a biodegradable polymer and a cationic detergent, removing the organic solvent from the emulsion and adsorbing the immunological adjuvant and the polynucleotide on the surface of the microparticle (claims 13, 15-21, 24-27, 30, and 31). With respect to the limitation of the size of the particles being between 200 nm and 20 μm, this is encompassed by the range recited in the application claim 42. The specification discloses that the polynucleotide can constitute 5% or 0.1 to 10% of the total weight of the microparticle (p. 8, column 1, paragraph 0091) and that the microparticles comprise 0.1 to 10% or 0.5 to 2 % cationic surfactant (p. 7, coliumn 2, paragraph 0087). Thus, the application claims 1-5, 8, 10, 11, 13, 15-21, 24-27, 30, and 31 anticipate claims 1-3, 5, 6, 9, 10, 12, 13, 15-18, 23, 26, 28-31, 34-37, 52-55, 61, 69, 76-79, and 86 of the instant application. Since the US Application No. 11/113,861 claims 1-5, 8, 10, 11, 13, 15-21, 24-27, 30, and 31 embrace all limitation of the instant claims, the patent claims and the instant claim are obvious variants of one another.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

5. Claim 50 provides for the use of the microparticle composition as a vaccine, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 50 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 40, 41 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a disclosure meets the

enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The Breadth of the Claims

The instant claims are drawn to (i) a method of treating a host animal having a pathogenic organism infection by administering to the animal a therapeutically effective amount of a microparticle composition comprising a biodegradable polymer, a cationic surfactant, and a polynucleotide adsorbed to the surface of the microparticle, and (ii) a method of immunizing a host animal against infection by a pathogenic organism by administering to the animal a microparticle composition comprising a biodegradable polymer, a cationic surfactant, and a polynucleotide adsorbed to the surface of the microparticle in an amount effective to induce a protective immune response.

As such, the as-filed specification attempts to claim that the disclosed immunogenic composition comprising any polynucleotide encoding for any polypeptide, can be employed as a master drug to treat infection by any pathogenic organism.

The aspects considered broad are (i) the range of pathogenic organisms and (ii) the range of polynucleotide to be used to induce a protective immune response. The broad term pathogenic organism is not limited in any way by the specification, and in fact encompasses known and unknown pathogenic organisms. Similarly, the broad term polynucleotide capable of inducing a protective immune response against a pathogenic organism encompasses a very wide range of polynucleotides encoding for various non-pathogen and pathogen-derived polypeptides that may or may not induce a protective immune response. It is noted that, although they can elicit an immune response, not all pathogenic polypetides are suitable to be used in vaccines to fight pathogenic infection. For example, Doria-Rose et al. (Methods, 2003, 31: 207-216) teach:

> "The first choice in designing a DNA vaccine is the target antigen.
>
> Another criterion for vaccine design is the ability of the antigen to modulate the immune response, specifically the T helper (Th) subtype.
>
> In general, Th1 responses are considered better for controlling intracellular pathogens, such as viruses; however, many viruses, such as rabies, can be controlled by antibody alone.
>
> [d]ifferent antigens are likely to be targets of humoral and cellular responses."

Therefore, one of skill in the art would not know that the claimed immunogenic composition, as broadly claimed, could be used to treat an infection caused by such a diverse range of pathogens.

The Nature of the Invention

The nature of the invention is a method of inducing a protective immune response by using a nucleic-acid-based vaccine.

The nature of such invention is within the broad genera of DNA immunization and DNA does not generally enable Applicants' invention due to problems with using nucleic acids-based vaccines as therapeutic agents. With respect to nucleic acid-based vaccines, Manoj et al. (Critical Reviews in Clinical Laboratory Sciences, 2004, 41: 1-39) teach:

> "Despite the numerous advantages described above, DNA vaccines have not been capable of inducing robust antigen-specific immune responses in large animals. Although DNA vaccines induce strong cellular immune responses, particularly the humoral responses are often not strong enough to confer protection from infection. This deficiency has been attributed to the relatively low transfection efficiency, which may be due to a number of factors.
>
> Conventional vaccines, such as subunit or killed vaccines, only depend on the host to induce an immune response to the antigen(s). DNA vaccines, however, depend on the host to first produce the antigen and then induce specific immune responses. Therefore, efficient transfection must first occur for DNA vaccines to produce sufficient quantities of antigen. Transfection of plasmids into eukaryotic cells in culture often results in high levels of protein production, mostly when used with products that facilitate the entry of the plasmid into the cells. However, when these eukaryotic cells are part of a larger system, such as the host, the plasmid appears to encounter difficulties in transfecting the cells. This emphasizes the need for improved vaccine delivery systems. Although a number of efforts have resulted in improved delivery of plasmid to mice, these approaches have not been as successful in large animals.
>
> In addition to transfecting few cells, the expression in individual cells may be low. Thus, the quantity of expressed antigen may not be sufficient to induce significant immune responses.
>
> If efficient transfection of the plasmid *in vivo* can be achieved, these imaginative strategies wiil contribute to providing the "final touches" for an outstanding DNA vaccine. However, for the present, the ability to cause significant numbers of plasmids to express sufficient amounts of protein should probably be the central focus in the development of DNA vaccines to help overcome some of their major limitation."

Given the teachings above, the Artisan would not know that a nucleic acid encoding for a polypeptide could be used to treat infection caused by pathogenic organisms or how to specifically deliver the nucleic acid to ensure a proper expression

of the immunogen to ensure an antibody response.

Hence, from the nature of the invention, the Artisan would not reasonably predict that the immunogenic composition claimed by the instant application could be used to induce a protective immune response against pathogenic organisms in general.

The State of the Prior Art and the Level of Predictability in the Art

Applicants contemplate to use the immune response induced by single antigen nucleic acid-based vaccines to treat patients affected with various pathogenic infections. However, at the time the invention was made, and even in the present, the art of using such single antigen vaccines to treat infectious disease was known to be unpredictable. For example, Doria-Rose et al. teach:

> "In HIV infection and related non-human primate models, only the envelope is targeted by neutralizing antibodies, whereas several other gene products may be targets of CTL. In addition, infected hosts develop unique individual CTL responses to viral gene products. This development may be due to the variability of the MHC genes in the outbred populations, such that different MHC haplotypes are able to present epitopes from a range of genes. Therefore, it is appropriate to use more than one antigen in an AIDS vaccine. Furthermore, HIV sequences vary tremendously; the inclusion of more antigens increases the chance of providing at least one that is cross-reactive with the circulating virus to which a given vaccine may be exposed. Such strategy has been successful for influenza, which mutates rapidly and has several circulating forms."

Therefore, at the time the instant invention was made, the therapeutic use of nucleic acids-based vaccines to treat pathogenic infections was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids-based vaccines *in vivo* (whole organism) in general (see above).

Given these teachings, the skilled artisan would not know *a priori* whether introduction of the claimed nucleic acid-based vaccine *in vivo* would result in a proper ommune response, and if so, whether the induced immune response would provide

successful therapy.

While the intent is not to say that nucleic acid-based vaccines can never be used to treat pathogenic infections, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given this unpredictability, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the claimed methods *in vivo* in all organisms, with a resultant induction of a protective immune response, as generally claimed.

The Amount of Direction or Guidance/The Existence of Working Examples

Given the breadth of the claimed invention, and the complexities associated with the nature of the claimed invention, one skilled in the art would have to turn to the specification for guidance. However, as indicated above, and even assuming that the level of one skilled in the art is relatively high in the prior art, the guidance provided by the specification is not sufficient to overcome the doubts and obstacles expressed in the art of record. As such, the only issue left is the working examples provided by the specification.

The specification provides one example of eliciting an immune response in mice immunized with microparticles comprising a plasmid DNA encoding for HIV p55. However, the specification does not provide examples of testing the instant immunogenic composition for its ability to treat HIV, or any other infections for this matter, in animal models or humans. The examples provided by the specification do not appear to reasonably render the claimed invention as a whole patentable under 35 USC, 112, first paragraph, particularly given the doubts expressed by numerous cited

art, as indicated above.

Given the diverse and unpredictable outcome of using the disclosed therapy method, the specification does not appear to provide sufficient guidance and/or working examples that specifically address the use of this method as being effective in treating pathogenic infections in a subject to enable one of ordinary skill in the art to use such identification method without undue experimentation.

Conclusion

Thus, the specification is not enabling for the claims of (i) of treating a host animal having a pathogenic organism infection by administering to the animal a therapeutically effective amount of a microparticle composition comprising a biodegradable polymer, a cationic surfactant, and a polynucleotide adsorbed to the surface of the microparticle and (ii) immunizing a host animal against infection by a pathogenic organism by administering to the animal a microparticle composition comprising a biodegradable polymer, a cationic surfactant, and a polynucleotide adsorbed to the surface of the microparticle in an amount effective to induce a protective immune response.

8. Claims 39, 42, and 44-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating an immune response in a host animal, does not reasonably provide enablement for stimulating an immune response with therapeutic purpose. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of stimulating an immune response in a host, by administering to the host microparticle composition comprising a biodegradable polymer, a cationic surfactant, and a polynucleotide adsorbed to the surface of the microparticle. Such language directed to stimulating an immune response is considered to embrace a composition efficient enough to elicit a protective immune response, when administered to a subject. Accordingly, preamble language directed to "stimulating an immune response" taken together with the disclosure that this means stimulating an immune response against a wide variety of antigens, is considered to require support as outlined in 35 U.S.C. § 112 first paragraph such that therapeutic benefit is considered to be enabled for one seeking to make and use such a composition (see the rejection of claims 40, 41 and 50 above).

9. Claim 38 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering a polynucleotide by administering to an animal a microparticle composition comprising a biodegradable polymer, a cationic surfactant, and a polynucleotide adsorbed to the surface of the microparticle, does not reasonably provide enablement for the delivery of a therapeutic amount of a polynucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make an/or use the invention commensurate in scope with these claims.

The instant claim is drawn to a method of delivering a therapeutic amount of a polynucleotide-containing species to a host animal by administering to the animal a microparticle composition comprising a biodegradable polymer, a cationic surfactant, and a polynucleotide adsorbed to the surface of the microparticle. Such language directed to delivering a "therapeutically amount of a polynucleotide-containing species" of the claimed composition is considered to embrace a composition efficient enough such that, when administered to a subject, the treatment of the subject having a condition associated with the composition is achieved. Accordingly, preamble language directed to "a therapeutic amount of a polynucleotide-containing species" taken together with the disclosure that the polynucleotides can encode for therapeutic proteins that is used to treat disorders such as cancer, is considered to require support as outlined in 35 U.S.C. § 112 first paragraph such that therapeutic benefit is considered to be enabled for one seeking to make and use such a composition.

The Breadth of the Claims

The aspects considered broad are: (i) the range of disorders to be treated, and (ii) the range of nucleic acids that can be used to treat disorders in general. As will be shown below, these broad aspects are not enabled.

The Nature of the Invention

The nature of the invention a method of using a composition comprising nucleic acids for preventing or treating disorders in general. The nature of such invention is within the broad genera of gene therapy and gene therapy does not generally enable

Applicants' invention due to problems with using nucleic acid-based therapies. For example, Meyer et al. (Review, Cell. Mol. Biol., 2001, 47: 1277-1294) teach:

> "Although gene therapy provides the hope and potential to revolutionize the future of medicine, this optimism must be tempered. Ongoing efforts to both quantitatively increase both gene transfer and expression to achieve improved therapeutic effect and to restrict the distribution and expression to relevant target tissues are under development. This includes enhancing the permeation of the vectors, development of targeted vectors that can be delivered systematically and regulating the level and target cell specificity of gene expression. Although these technologies are under development, advances in these areas will further improve the efficacy and safety of gene therapy vectors and further increase chances of success."

Hence, from the nature of the invention, the Artisan would not reasonably predict that the nucleic acids claimed by the instant application could be used to prevent, treat or even alleviate disorders in general.

The State of the Prior Art and the Level of Predictability in the Art

At the time the invention was made, and even in the present, the art of treating disorders using nucleic acids was known to be unpredictable with respect to efficacy of delivering the nucleic acids to the targeted cells or tissues and a prolong expression of the therapeutic gene of interest.

The problems of nucleic acids based therapies are well known in the art, particularly with regard to the delivery systems, the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is expressed to a degree necessary to result in a therapeutic effect.

For example, with respect to specific delivery and gene expression, Fisher A. (Review, Cell. Mol. Biol., 2001, 47: 1269-1275) teaches:

> "In spite of its logic, this therapeutic approach is complex considering the manner in which one must search in order to obtain a prolong expression of the therapeutic protein of interest. This objective contains several barriers: the difficulty in many cases of

> targeting cells (for example, the epithelial cells of the respiratory tract or of muscular fibers), the life duration of these cells, and the loss of expression of the transgene which is linked to several factors.
> The cancer represents the principle domain of assays for the application of gene therapy.
> Until today, the results have been rather deceiving, essentially because of the feeble efficiency of targeting the cells. In any case, gene therapy for cancer cannot be conceived without being combined with "classic" treatments: chemotherapy, radiation, and surgery.
>
> For ten years, about 500 clinical gene therapy trials have been undertaken globally, with 80% of them occurring in the United States. Despite the fact that many of these experiments are more interested in issues of tolerance and pharmacology (phase I/II) that in efficacy, only very few have provided any proof of efficacy as of yet. Actually, this is easily explained by the difficulties of this therapeutic approach: it is necessary to obtain the expression of a potentially therapeutic gene that requires a good understanding of the disease's physiopathology in the targeted cells, at a level that is neither too low (efficacy) nor too high (toxicity). Ten years of clinical trials tests is not very much! It is true, however, that many actors in the research have largely underestimated the encountered difficulties."

With respect to the problems encountered with the delivery systems, Gardlik et al. (Review, Med. Sci. Monit., 2005, 11: RA110-121) teach:

> "The simplest way of gene delivery is injecting naked DNA encoding the therapeutic protein, but because of low efficiency there is a need to use special molecules and methods to improve gene delivery.
>
> Two kinds of vectors have been employed as vehicles for gene transfer. Viral vectors for gene transduction, such as retroviral, adenoviral, and adeno-associated viral vectors, and non-viral vectors for gene transfection, such as plasmids and liposomes. However, each vector has its own advantages and disadvantages: none of these types of vectors has been found to be ideal for both safe and efficient gene transfer and stable and sufficient gene expression"

Therefore, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) in general. Such obstacles include, for example, problems with delivery, target accessibility and stable and sufficient protein expression.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of nucleic acids *in vivo* by the broadly disclosed methodologies of the instant invention, would result nucleic acids reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful therapy. One of skill in the art would not know how to deliver nucleic acids to an organism in such a way that would ensure an amount sufficient to stably and sufficiently express the therapeutic gene in the proper cell.

While the intent is not to say that nucleic acids can never be used in gene therapy, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given this unpredictability, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the claimed methods *in vivo* in all organisms, with a resultant prevention or treatment of diseases, as broadly claimed.

In fact, the state of the art is such that successful delivery of nucleic acids *in vivo* or *in vitro*, such that they provide the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of gene therapy using nucleic acids in general *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, treat diseases in general.

The Amount of Direction or Guidance/The Existence of Working Examples

The specification does not provide the guidance or the working examples required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The field of nucleic acids therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods. In order to practice the claimed invention in its full claimed scope *in vivo* in all organisms a number of variables would have to be optimized, including: (i) the mode of delivery of nucleic acids to an organism that would allow it to reach the targeted cell, (ii) the amount of nucleic acid that would need to be delivered in order to express a stable and sufficient amount of the therapeutic gene for prevention or treatment, once it reached the proper cell, and (iii) ensuring that the nucleic acid remains viable in a cell for a period of time that allows expression to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each nucleic acid. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation.

Conclusion

Thus, the specification is only enabling for a method of delivering a polynucleotide by administering to an animal a microparticle composition comprising a biodegradable polymer, a cationic surfactant, and a polynucleotide adsorbed to the

surface of the microparticle, and not for a method of delivering a therapeutic amount of polynucleotide.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-3, 5, 6, 9, 10, 12, 13, 15-18, 23, 26, 28-31, 34-42, 44-48, 50, 52-55, 61, 69, 76-79, and 86 are rejected under 35 U.S.C. 102(e) as being anticipated by O'Hagan et al. (U.S. Patent No. 6,884,435)

The applied reference has a common inverntor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

O'Hagan et al. teach (i) a microparticle comprising a polymer such as PLG, a cationic detergent such as CTAB, and an antigen comprising a polynucleotide such as plasmid (example 7 discloses that the plasmid is pCMV) adsorbed on the surface of the

microparticle, wherein the polynucleotide encodes for an antigen derived from a pathogenic organism such as HIV and wherein the microparticle is formed in the presence of the detergent and then exposed to the polynucleotide (the specification defines that a w/o/w solvent evaporation system can be used to form the microparticles, see column 13, lines 10-39); the microparticles further comprise CpG as an immunological adjuvant (claims 1, 5-13, 16, 17, 19, 20, 24-26, 35-37) and (ii) a method for raising an immune response by administering the microparticles to a vertebrate animal (the specification discloses that the intent of delivery is to use the particle as a vaccine to elicit an immune response in a vertebrate and to treat a disease, see column 4, lines 3-30; additionally the specification defines that a vertebrate can be a human, column 8, lines 45-52) (claims 38-40). The specification discloses that the polynucleotide can constitute 5% or 0.1 to 10% of the total weight of the microparticle (column 14, lines 6-10) and that the microparticles comprise 0.1 to 10% or 0.5 to 2 % cationic surfactant (column 13, lines 30-37). With respect to the limitation of the adjuvant being adsorbed on the surface of the microparticle, the specification discloses that adjuvants can be used to enhance the immunogenicity of the microparticles and that the adjuvants can be adsorbed on the microparticles (column 14, lines 36-51). With respect to the limitation recited in claim 3, the specification discloses that the microparticles have a diameter of about 200 nm to about 30 μm that includes the range recited by claim 3 (column 5, lines 1-10). Since O'Hagan et al. teach all limitation of the instant claims, the instant invention is anticioated by the above-cited art.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 27-31, 34-39, 42, 44-48, 52-55, 61, and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Proc Natl Acad Sci USA, 2000, 97: 811-816).

Singh et al. teach microparticles comprising PLG, CTAB, and a polynucleotide-containing species that is adsorbed on the surface of the microparticles, wherein the polynucleotide-containing species is pCMV (i.e., the first polynucleotide-containing species comprisies CpG, therefore, the microparticle composition comprises an immunological adjuvant that is CpG) encoding for HIV p55gag; the microparticles are made by forming a w/o/w emulsion between PLG and CTAB, removing the solvent from the emulsion and adsorbing pCMV to the resultant microparticles, wherein the CTAB is not removed from the microparticles, and the microparticles thus made are used to inject mice (i.e, they are in a pharmaceutically acceptable excipient) (p. 811, column 1 bridging column 2, p. 812 column 1). Singh et al. suggest the use of these psrticles in humans)p. 815, column 2, third paragraph). With respect to the limitations of the microparticles having a diameter between 200 nm and 20 μm (claim 3), of the first polynucleotide-containing species constituting at least 5% (claim 1), 10-30% (claim 27) or 10-20% (claim 28) and of the microparticles comprising 0.1-10 wt% (claim 29) or 0.5-

2 wt% (claim 30) cationic surfactant, absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. The following is a citation from MPEP:

2144.05 [R-3] Obviousness of Ranges

II. OPTIMIZATION OF RANGES
A. Optimization Within Prior Art Conditions or Through Routine Experimentation
Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).
B. Only Result-Effective Variables Can Be Optimized
A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

Claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 23, 27-31, 34-39, 42, 44-48, 52-55, 61, 69, and 76-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Proc Natl Acad Sci USA, 2000, 97: 811-816), as applied to claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 27-31, 34-39, 42, 44-48, 52-55, 61, and 69 above, in view of Thalhamer et al. (Endocrine Regulations, 2001, 35: 143-166), as evidenced by Diwan et al. (Journal of Controlled Release, 2002, 85: 247-262).

Singh et al. do not teach microparticles further comprising an adsorbed CpG as an immunological adjuvant. However, at the time the invention was made, the use of CpG adjuvants in combination with DNA vaccines was already known in the art. For example, Thalhamer et al. teach the usefulness of CpG adjuvants to expand the range of possible immune regulations (p. 158, column 1, second paragraph). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to further adsorb CpG oligonucleotide (negatively charged) to the already made cationic microparticles, with a reasonable expectation of success. The motivation to do so is provided by Thalhamer et al. who teach that CpG adjuvants directly and indirectly stimulate different cells of the immune system such as APC and induce large amounts of IL-2, which is important for mediating Th1 immune reactions, which in turn promotes CTL development (p. 158, column 1, third paragraph). One of ordinary skill in the art would have been expected to have a reasonable expectation of success in making and using such because the art teaches the successful use of such combinations (see Diwan et al.). Thus, the claimed invention was prima facie obvious at the time the invention was made.

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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